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Neural Circuits Underlying Parental Behavior

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Abstract

Parental care, including feeding and protection of young, is essential for the survival as well as mental and physical well-being of the offspring. Recent studies have began to uncover key brain areas and neuron types involved in the control of social interactions with infants, thus offering new opportunities to understand, in mechanistic terms, the function and modulation of circuits underlying parental care in males and females, across species, and in various physiological and environmental conditions.

One Sentence Summary

We review the identification of the neural circuits underlying affiliative and agonistic behavior of males and females toward young, and the physiological and hormonal factors that modulate their function.

Parental behavior aims at caring for conspecific young and increasing their survival. Ranging from egg-laying site selection, nest building, burrowing, egg attending, brooding and carrying the young in oviparous animals to food provisioning, nursing, defending offspring, and even teaching skills in viviparous animals, parenting occurs in a surprisingly high variety of vertebrates and invertebrates including insects, arachnids, mollusks, fishes, amphibians, reptiles, birds and mammals. In mammals, mothers commonly take the primary responsibility of parental care, whereas fathers often ignore or even attack the young. However, in many species, direct engagement of fathers is seen, ranging from small to equal and even exclusive participation in parental duties (Figure 1).

Nurturing and affiliative behavior toward infants is highly sensitive to physiological and environmental factors such as stress and hormone levels, and, in humans, the quality of parental care is affected by stress and mental illnesses such as post-partum depression (PPD), which affects over 10% of mothers in the US (*1*). How is the diversity of parental behavior generated in males and females, across different species, and in various physiological or pathological conditions? Recent studies have begun to uncover the nature and function of circuits underlying parental interactions with young. We review here data suggesting the existence of highly conserved and antagonistic circuits controlling affiliative and aggressive behavior towards offspring, respectively. Remarkably, circuits underlying these opposing behaviors are present in both male and female brains, irrespective of the normal expression of parenting displays, and are highly modulated by intrinsic and environmental factors.

Diversity in Parental Care

Parental care has evolved repeatedly across invertebrate and vertebrate taxa (*2*). The involvement of males or females (or both) in the care for offspring varies across taxa and even between populations within a species (Figure 2). In many systems, who cares for offspring can be partially correlated with certainty in parentage and/or adult sex ratio. In mammals, internal fertilization that ensures maternity, but not paternity, coupled with the restriction of lactation to females, makes male involvement rare (*3*). Remarkably, in some rodents, canids, and primates, males assist and invest significantly in the care of offspring (*4–8*), while closely related species are exclusively maternal (*9–12*). For example, prairie voles and California mice are biparental with males showing all female-typical parental displays except nursing (*4*, *5*), while closely related species in the same genus, such as the montane vole, meadow vole, or deer mice, are female uniparental (*9–12*). Cross fostering experiments showed that meadow vole males reared by biparental prairie voles exhibited significantly more paternal care to their offspring than in-fostered counterparts (*13*). This result demonstrates the influence of early social environment on parental behavior in addition to genetic differences between congeneric species.

Male involvement in offspring care is also common in many taxa other than mammals. In teleost fish species, males provide care more often than females, including nest building and egg attendance (*14*). In a well-known case of the three-spined stickleback, males set up the territory, build nests and defend their offspring (*15*). In birds, 90% of the species are biparental with both parents sharing the responsibilities of building a nest, incubating eggs, and defending and feeding the young (*16*). The sex ratio of individuals available to mate in a bird population largely determines which parent cares for offspring. For example male shorebirds are more likely to care for offspring in populations where males are more abundant than females (*17*).

Amphibians display striking diversity in parental care. Many species of anurans and salamanders display care for offspring beyond egg laying, with roughly 50 independent evolutionary transitions to parental care (*18*). The diversity of parental care employed by amphibians is also stunning, from foam nests (*19*), egg guarding, transport of offspring piggyback style (*20*), to diverse methods of egg incubation in dorsal pouches, vocal sacs or stomach. South American poison frogs (*Dendrobatidae*) show particularly striking differences in which sex cares for offspring within closely related species (*21*).

Such natural diversity in parental care strategies across large evolutionary distances, as well as in related species and in individuals within a species, suggests the existence of conserved neural pathways underlying parental care that are differentially regulated in males, females and in different species.

Sensory cues that drive parental interactions

Neuroethologists have long recognized intriguing differences in the nature and complexity of signals driving parental behaviors. In fish and birds, social behaviors including care of young were often seen to be triggered by simple cues (*22*). The domestic hen for example comes to the immediate rescue of a chick after hearing its distress call, but the sight of a struggling chick without sounds leaves the fowl indifferent (*23*). In turn, the reliance on simple visual signals in some species of birds generates the so-called "supernormal" stimulus effect in which artificial stimuli with exaggerated features such as higher contrast pigmentation or giant sizes are even more effective at eliciting parental behavior than natural eggs (*22*).

In mammals, multiple sensory modalities have been shown to trigger maternal responses. Early studies in rats (*24*), found that blind, anosmic or anaptic lactating females, each retrieve pups in a fashion not significantly different from controls. However, the combination of anosmia and tactile deprivation results in more pronounced defects in retrieving than does the loss of either sensory system alone, and the defects are even more severe when all three sensory inputs were eliminated. Interestingly, different sensory modalities appear to often synergize with each other, and perform critical roles in different steps of the parental response.

In rodents, low frequency wriggling calls emitted by pups when they struggle in the nest induce licking, change of suckling position and nest building by the mother (*25*). In contrast, ultrasonic vocalizations produced by pups lost outside the nest trigger immediate search for, and retrieval of the isolated pups to the nest (*26*), with retrieval occurring even if the ultrasonic vocalizations have ceased. Intriguingly, mouse fathers can be induced to display fast pup retrieving behavior by 38-kHz ultrasonic vocalization from their female partners (*27*).

Chemosensory cues are extensively used to elicit or inhibit parental care according to the gender and physiological status of the animal. Many amphibians, fish, birds, and insects, such as ants or the burrowing bug were shown to use olfactory cues to recognize offspring (*28-31*). In many mammals, the vomeronasal pathway, in conjunction with the olfactory system for some species, inhibits parental behavior and drives pup-mediated aggression in virgin animals, while olfactory cues are often seen facilitating the care of offspring in parents or primed animals (*32*). Virgin rats initially find foreign pups aversive but exhibit parental care after continuous exposure to the pups (*33*). Surgical removal of the VNO reduces infanticidal behavior and induces faster paternal behavior (*34*), while olfactory cues emitted by pups appear to facilitate parental care (*32*, *35*). Recent studies in mice confirmed that surgical or genetic VNO loss of function leads to dramatic reduction in pup-directed aggression and to the emergence of parental care in virgin males (*36*, *37*). In humans, one study documented a much higher rating of infant body odors by postpartum mothers than nulliparous women (*38*), and odors have been proposed as significant cues in early interactions between mothers and infants (*39*, *40*).

A fascinating example of multisensory interaction comes from the mother-infant bonding in sheep (*41*). Olfactory cues are responsible for both inhibiting maternal responsiveness of ewes before parturition, and for attraction to amniotic fluid immediately after parturition (*42*). Shortly after pregnant ewes give birth, a selective bonding between the mother and the infants rapidly develops, such that ewes only nurse their own offspring and behave aggressively toward alien young. However, artificial vaginocervical stimulation that mimics the expulsion of the lamb resets the ewe's olfactory preference towards an alien lamb, likely through oxytocin release.

The sensing of infant cues is remarkably enhanced in parents, and parturition and maternal care have been associated with multisensory facilitation and extensive cortical plasticity.

Recordings of ultrasonic calls played to lactating female rodents showed that searching behavior is facilitated by pup vocalizations in the presence of olfactory cues (*43*, *44*). Neuron responses and population dynamics in the auditory cortex undergo significant changes in mothers compared to virgin female mice, likely facilitating the representation of pup vocalizations and enhancing their behavioral relevance (*45*–*48*). Moreover, a significant modulation of sound evoked-responses by pup odors has been shown in the primary auditory cortex of lactating female mice shortly after parturition, with neurons from lactating mothers displaying more sensitivity to sounds than virgins (*47*). In the olfactory system, mitral cells in the olfactory bulb of female ewes have been shown to undergo dramatic changes in sensory responses to lamb versus food odors after parturation (*49*, *50*). Moreover, in vivo time-lapse imaging of adult newly-born granule cells in mice showed an enhanced integration of these neurons into the olfactory circuit of lactating mothers (*49*).

Switching between parental care and aggression

Infant-directed aggression is prevalent in animals that are not rearing offspring such as virgin animals, and in sexually mature stranger males (*51*), and it is often seen to switch into affiliative behavior after birth of offspring or habituation to the young. Thus, adult animals may display parental care or aggression according to their physiological and environmental state, and the regulation of affiliative versus agonistic behavior circuits raises an important and fascinating question in the study of parental interactions.

In laboratory mice, infanticide is commonly observed in virgin males (*52*). Males stop committing infanticide and become paternal toward pups in a transient period after mating with a female, starting at the approximate time of birth until the weaning of pups (Figure 3) (*53*). The coincidence of the suppression of infanticide in males and the birth of their own pups likely provides an adaptive mechanism that prevents a male mouse from killing its own pups, but successfully eliminates pups sired by competing males. Parental males and females, however, do not appear to differ in the overall incidence of retrieving, nest building, licking, and huddling over the pups (*54*). Interestingly, wild-caught female mice are typically infanticidal, and they follow a similar transition to parental care associated with parturition and lactation, with a surprising elevation of infanticide throughout pregnancy (*55*, *56*). The drastic difference between laboratory and wild female mice suggests that infanticide was selected out by colony breeding in females.

Time-dependent synaptic or transcriptional change triggered by mating, as well as the chemical cues released by females during pregnancy (*57*) have been hypothesized to drive the radical behavior shift from infanticide to parental behavior (*53*, *58–60*). The timing and mechanism of the mating-induced behavioral switch in mice has been assessed by two recent studies (*36*, *37*). Following pup exposure neurons in the vomeronasal pathway appear more strongly activated in virgin males than in fathers (*36*), and impairment of VNO sensing results in decreased pup-directed aggression and induction of parental care (*36*, *37*). These results raise the intriguing possibility that the transition of attack to parenting could be due to a time-dependent reduction of vomeronasal activation by pup cues in males.

The intriguing temporal switch in offspring recognition associated with mating is not restricted to rodents; it has been observed and characterized in a variety of species including isopods, burying beetles, African cichlids and birds (*61*).

Neural circuits underlying parental interactions

Much of our knowledge about neural circuits underlying parental behavior comes from studies in rats, with recent insights provided by genetic studies in mice. In contrast to lactating females, which are highly maternal, virgin male and female rats usually avoid physical contact with foreign pups. Nonetheless, after continuous exposure to pups, virgin males and females approach, interact with them and eventually exhibit parental care, in a process termed "sensitization" (*33*).

The dramatic changes in female hormone levels including estrogen, progesterone and prolactin through pregnancy have been long implicated in the regulation of maternal behavior (*62*). Virgin females treated with a regimen mimicking this pattern facilitates the display of maternal behavior (*63*). Moreover, recent genetic studies have shown that the prolactin receptor is essential for the normal display of maternal behavior (*64*). Prolactin is also an important regulator of parental care in non-mammalian vertebrates, most notably in birds and teleost fish where prolactin rises during egg laying/spawning and remains elevated throughout the duration of parental care (*65*, *66*).

Male interaction with infants is also influenced by hormonal changes (*67*). In many vertebrate species where males are involved in offspring care, testosterone levels decrease during fatherhood in humans, frogs, and fish (68-*70*). The intrauterine position, and therefore the early exposure to different levels of sex hormones has been proposed to influence the pup-directed aggression in later adulthood in mice (*71*). In addition, progesterone receptor knockout virgin male mice were shown to exhibit little aggression but elevated parental care towards foster pups (*72*).

The contrast between caring by parents and aversion by virgin animals has led to search for brain areas involved in the stimulation and inhibition of maternal behavior (*73*) (Figure 4). Classical mapping experiments have demonstrated the essential role of several brain areas in the control of maternal behavior, including the medial preoptic area (MPOA) and the adjacent ventral bed nucleus of stria terminalis (vBNST) (Figure 4A) (*73*, *74*). A combination of IEG mapping and tracing further mapped the projection sites of the active MPOA/vBNST neurons (Figure 4A) (*75*). In addition to the preoptic area, the lateral septum has also been involved in the regulation of parental care (*76*), and both areas have been implicated by IEG studies in the paternal care of biparental rodents (*77*) and biparental cichlid fish (*78*). Electrical stimulation of the preoptic area in male bluegill sunfish also elicits paternal care (*79*). These results suggest that highly conserved circuits and neuroendocrine mechanisms may be repeatedly recruited to mediate similar social behaviors (*2*, *80*). What specific information is carried by these brain regions and how they encode the various components of parental care remain to be determined.

A similar set of experiments uncovered a parallel neural system that inhibits maternal behavior, thus opposing the function of the pathways described above (Figure 4B). In particular, the medial amygdala (MeA), which receives direct projection from the accessory olfactory bulb (AOB), was shown to mediate the suppression of maternal care and the initial avoidance responses in virgin female rats (*81*). A number of other brain areas, many of them interconnected and involved in defensive social encounters were also shown to inhibit maternal responses (*82*, *83*), suggesting that pup aversion may share common circuitry with defensive behavior.

From these studies, a hypothetical neural model of the control of parental behavior in rats has been proposed, according to which two competing pathways mediate active maternal responses and aversive behavior towards pups, respectively (*84*, *85*). In male and most female virgin rats, the aversive circuit, primarily innervated by vomeronasal inputs, is dominant and suppresses parental care, whereas in postpartum and "sensitized" females, hormonal, neuromodulatory and experience-dependent factors activate the facilitative circuit and silence the avoidance circuit. Uncovering how these two conflicting circuits are differentially modulated in different physiological or environmental conditions is therefore central to the understanding of the control of parental care in males and females of various species.

The ventral tegmental area (VTA) is a major dopaminergic area that is involved in reward and reinforcement learning. Pups are known to be reinforcing stimulus to postpartum females (*86*), and MPOA lesions were found to disrupt the performance of an associative learning task using pups as positive reinforcement (*87*). Moreover, inactivation of VTA projections disrupts maternal behavior in postpartum rats (*88*), and depletion of dopamine in the ventral striatum or lesion of dopamine neurons in the VTA causes a persistent deficiency in pup retrieval (*89*, *90*). These results suggest that the dopaminergic system helps initiate and maintain maternal behavior in rats, likely by engaging the MPOA (*74*).

Targeted disruption of the dopamine β-hydroxylase (*Dbh*) gene, which synthesizes noradrenaline and adrenaline, leads to severe defects in maternal behavior (*91*). Intriguingly, providing noradrenaline precursor at the time of parturition is sufficient to restore maternal behavior in *Dbh* mutant females and maintain maternal care toward their future litters, suggesting that noradrenaline is critical at birth for the formation of a stable behavioral memory, which in turn is responsible for the maintenance of maternal care (*91*, *92*).

The role of the serotonergic system was recently demonstrated by the maternal defects of Pet-1 (an ETS transcription factor whose brain expression is limited to serotonin neurons) knockout mice, in which serotonergic gene expression and serotonin synthesis are greatly reduced (*93*). The MPOA and the BNST are innervated by serotonin-immunoreactive fibers (*94*), suggesting that the maternal deficiency may result from impaired serotonin inputs to these areas.

The highly conserved neuropeptide, oxytocin, is also an essential regulator of parental care across animals (reviewed by L.J. Young, this issue). Female mice deficient in oxytocin are unable to nurse, although they display largely normal maternal behavior (*95*). Studies using oxytocin receptor knockout females found no obvious deficits in their maternal care (*96*), but a recent reexamination of their behavior suggested that oxytocin is involved in the initiation, but not the maintenance of maternal behavior (*97*). In addition to mammals, the function of oxytocin appears to also extend to other vertebrate systems including birds (*98*) and fish (*70*).

The brain regions involved in the control of parental behavior are highly heterogeneous structures, and newly designed molecular and genetic tools make it possible to identify and functionally manipulate precise subsets of neurons, thus enabling a deeper understanding of the associated behavior circuits.

A recent study uncovered a subset of MPOA neurons expressing the neuropeptide galanin that are specifically activated during male and female parenting (Figure 5A) (*37*). Specific ablation of MPOA galanin neurons in virgin females, mothers and fathers results in dramatic impairment of parental responses and induced pup-directed aggression in virgin females (Figure 5B, C). In contrast, optogenetic activation of these neurons in virgin males suppresses pup-directed aggression and induces pup grooming (Figure 5D). These results suggest a direct role of MPOA galanin neurons in activating parental responses and confirm the suspected reciprocal inhibition between circuits activating and repressing parental behavior. The identification of MPOA galanin neurons as an essential regulatory node of male and female parenting behavior provides a precious entry point for further dissection of behavior circuits underlying parental care and their modulation by social experience.

In conclusion, emerging evidence suggests that highly conserved circuits and modulatory mechanisms may exist across species and in both male and female brains to regulate parental interactions with offspring. Remarkably, the natural behavior of adults towards infants emerges as the mutually exclusive output of two highly regulated circuits driving affiliative versus aversive responses. Future studies should exploit the natural diversity of parental systems across animal species to gain mechanistic insights into the regulation of parental behavior in physiologically and ecologically relevant contexts. This in turn, is likely to shed new light onto the complexity of human parental behavior and its susceptibility to mental illness.

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Figure legends

Figure 1. Paternal care can be observed in many different taxa. Species and photo credits: **A.** Giant water bug (*Abedus herberti*), Ivan Phillipsen; B. Los Tayos rocket frog (*Hyloxalus nexipus*), Adam Stuckert; C. Silverback gorilla (*Gorilla beringei*) father with infants, Lubert Stryer.

Figure 2. Evolution of diverse and distinct parental cares strategies across the animal kingdom. Examples of different parental care strategies are shown across vertebrates and invertebrates. Male uniparental care is lacking only in the mammalian and reptilian lineages, although there are male-biased parental care systems in few canids and primates. Photo credits and full names in online information.

Figure 3. Pup-directed behavior of males at different days after mating (re-plotted from Table 2 in Vom Saal, 1985).

Adult CF-1 males were mated with females, randomly assigned into groups and tested at different days after mating. Control virgin males are plotted at Day 0. After a significant increase in pup-directed aggression at Day 4, there is a transient suppression of attack and increase in paternal care in the males from Day 12 to Day 50, which approximately corresponds to the birth of and the weaning of their own pups. This experiment illustrates a remarkable influence of mating on male parental behavior.

Figure 4. Schematic presentation of brain areas associated with parental care (A) and pup-directed avoidance and aggression (B).

Solid lines denote projections that are involved in the regulation of pup-directed behavior supported by direct evidence. Dashed lines denote known connections that exist between these areas, and potentially involved in the behavior. The lines and arrows simply denote origins and targets and do not stand for actual axon path or excitatory inputs. Not all the known connections are shown. Abbreviations of brain areas provided in online information.

Figure 5. MPOA *Gal* neurons serve as an essential regulatory node for parental care in both male and female mice.

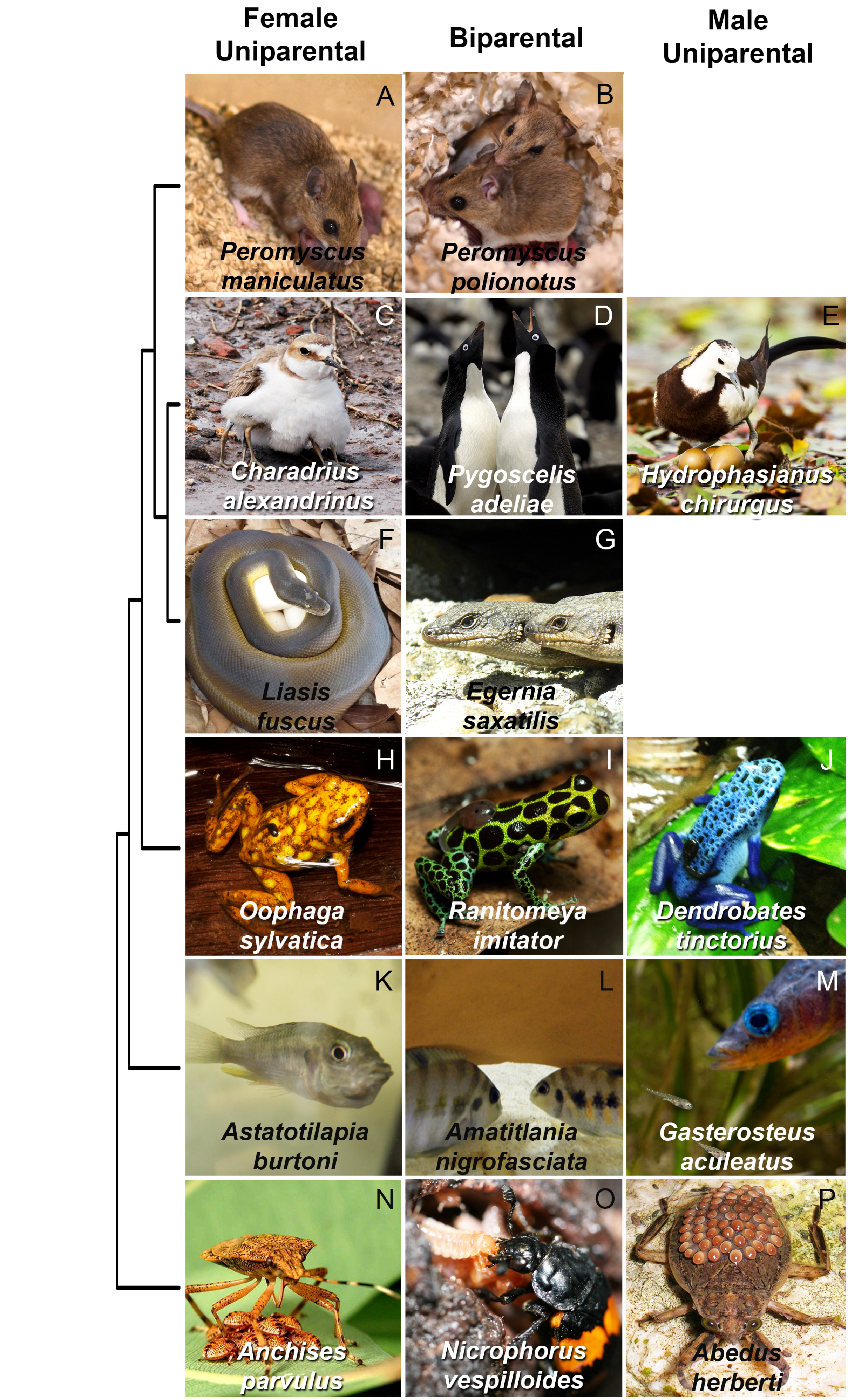
A. Co-labeling of *c-fos* and *Gal* in the MPOA of parenting females. B. Cumulative percentages of virgin females that retrieved or attacked pups as a function of the percentage of remaining *Gal* cells after *Gal* cell ablation. Reference cell number (100%) is the average MPOA *Gal* cell number in the control group. C. Cumulative percentages of fathers that retrieved pups as a function of remaining *Gal* cells after *Gal* cell ablation. D. Behavior raster plots after optogenetic activation of *Gal* cells in virgin males interacting with pups. Control group consisted of cre negative littermates with similar light stimulation. Different behavior elements are color coded and could occur simultaneously.

Online information

Figure 2. Evolution of diverse and distinct parental cares strategies across the animal kingdom. Species names and photo credits: A. Common deer mouse (*Peromyscus maniculatus*), Andrés Bendesky; B. Oldfield mouse (*Peromyscus polionotus*), Andrés Bendesky; C. Kentish Plover, Pinjia Que; D. Adélie penguin (*Pygoscelis adeliae*), Oliver Kruger; E. Pheasant-tailed Jacana (*Hydrophasianus chirurgus*), Ghulam Rasool; F. Water python (*Liasis fuscus*), Dale DeNardo; G. Black Rock Skink (*Egernia saxatilis*), Alan Couch; H. Diablito Frog (*Oophaga sylvatica*), Elicio Tapia; I. Mimic Poison Frog (*Ranitomeya imitator*), Evan Twomey; J. Dyeing Poison Frog (*Dendrobates tinctorius*), Lauren O'Connell; K. Burton's Mouthbrooder (*Astatotilapia burtoni*), Rayna Harris; L. Convict cichlid (*Amatitlania nigrofasciata*), Bryan Matthews; M. Three-Spined Stickleback (*Gasterosteus aculeatus*), Dwight Kuhn; N. Golden Brown Stink Bug (*Anchises parvulus*), Peter Chew; O. Burying Beetle (*Nicrophorus vespilloides*), Allen Moore; P. Giant Water Bug (*Abedus herberti*), Michael Bogan.

Figure 4. Schematic presentation of brain areas associated with parental care (A) and pup-directed avoidance and aggression (B). Abbreviations of brain areas: MOB, main olfactory bulb; PFC, prefrontal cortex; NAc, Nucleus Accumbuns; VP, ventral pallidum; LSd, lateral septum, dorsal part; LSi, lateral septum, intermediate part; vBNST, bed nucleus of stria terminalis, ventral part; MPOA, medial preoptic area; PVNm, paraventricular nucleus, magnocellular part; BL, basolateral amygdala; Ce, central amygdala; VTA, ventral tegmental area; PAG, periaqueductal gray; Raphe, Raphe nucleus; LC, locus coeruleus; AOB, accessory olfactory bulb; LSv, lateral septum, ventral part; BNSTpr, bed nucleus of stria terminalis, principal nucleus; PVNp, paraventricular nucleus, parvocellular part; DMH, dorsomedial hypothalamic nucleus; VMH ventromedial hypothalamic nucleus; MeA, medial amygdala; PMd, premammillary nucleus, dorsal part.


A
B
C


Female Uniparental
Biparental
Male Uniparental
A
Peromyscus maniculatus
B
Peromyscus polionotus
C
Charadrius alexandrinus
D
Pygoscelis adeliae
E
Hydrophasianus chirurgus
F
Liasis fuscus
G
Egernia saxatilis
H
Oophaga sylvatica
I
Ranitomeya imitator
J
Dendrobates tinctorius
K
Astatotilapia burtoni
L
Amatitlania nigrofasciata
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Gasterosteus aculeatus
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Anchises parvulus
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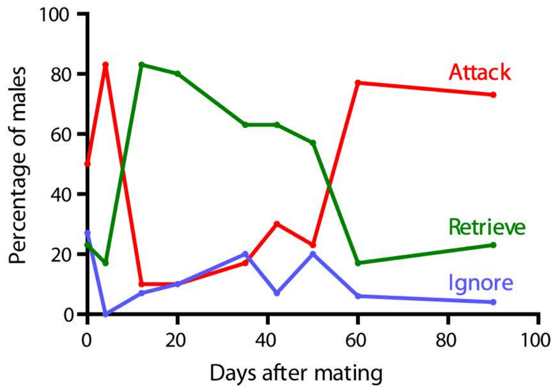
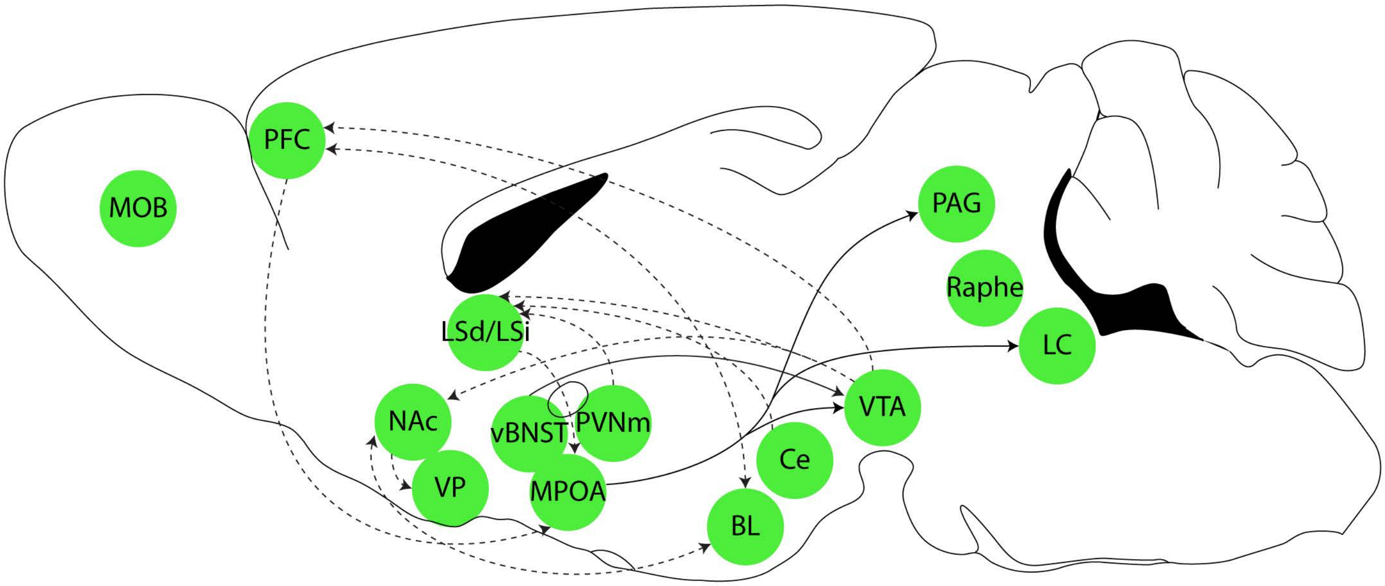
Nicrophorus vespilloides
P
Abedus herberti



100
80
60
40
20
0
Percentage of males
0
20
40
60
80
100
Days after mating
Attack
Retrieve
Ignore

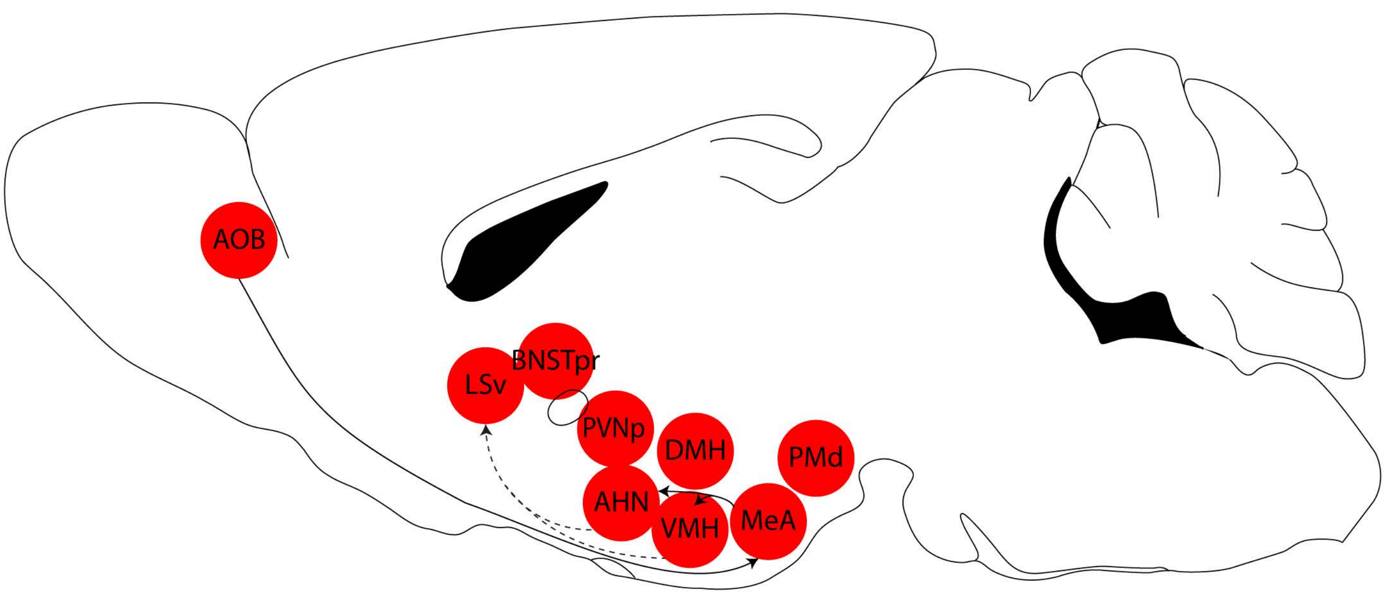
A

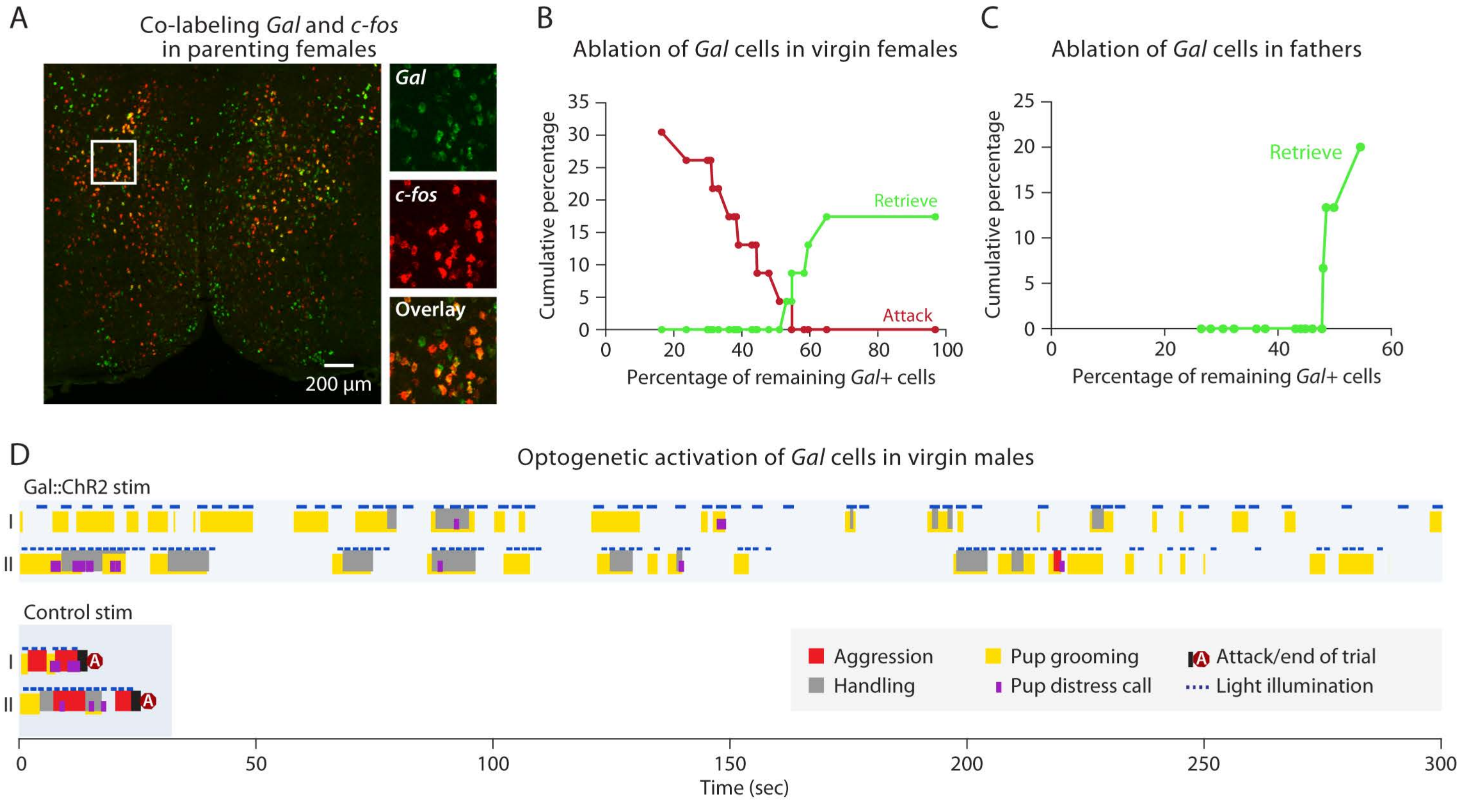
Brain areas associated with parental care



B

Brain areas associated with pup-directed avoidance and aggression




A
Co-labeling Gal and c-fos
in parenting females
Gal
c-fos
Overlay
200 µm
B
Ablation of Gal cells in virgin females
Cumulative percentage
Retrieve
Attack
Percentage of remaining Gal+ cells
C
Ablation of Gal cells in fathers
Cumulative percentage
Retrieve
Percentage of remaining Gal+ cells
D
Optogenetic activation of Gal cells in virgin males
Gal::ChR2 stim
I
II
Control stim
Aggression
Handling
Pup grooming
Pup distress call
Attack/end of trial
Light illumination
Time (sec)